The response is timely filed, and therefore Applicants believe no fees are due in connection with this response. However, the Commissioner is authorized to charge any necessary fees or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

AMENDMENT

In the claims:

Please amend claims 1-4, so that the text of the amended claims reads as follows. Please add new claims 5-7.

1.(Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:4; and

(b) hybridizes under highly stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 3.

B1

2.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 4.

3.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 2.

4.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 6.

5.(New) A cell comprising the expression vector of Claim 2.

B2

6.(New) A cell comprising the expression vector of Claim 3.

7.(New) A cell comprising the expression vector of Claim 4.

RESPONSE

I. Status of the Claims

No claims have been canceled. Claim 1-4 have been amended. New claims 5-7 have been added. Claims 1-7 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Claims

Claim 1 has been amended to further clarify the claim, and to recite that the stringent hybridization conditions are highly stringent hybridization conditions. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 1 as originally filed and at page 7, lines 8-15.

Claims 2-4 have been amended to further clarify the claims.
Support for these claims can be found throughout the specification as originally filed, with particular support being found at least in claims 2-4 as originally filed and at page 15, line 36-page 16, line 4.

New claims 5-7 have been added to more clearly claim aspects of the invention. Claims 5-7 find support throughout the specification as originally filed, with particular support being found at page 16, lines 4-20.

As the amendments to claims 1-4 and new claims 5-7 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Objection to Oath/Declaration

The Action objects to the oath or declaration as defective, because it allegedly fails to identify the citizenship of inventor N. Wilganowski. Applicants believe that this objection has been addressed in a response to a Notice to File Missing Parts, mailed, after the Action, on 6/18/02. In that Response to Missing Parts, (mailed on 8/16/02) inventor N. Wilganowski's citizenship was identified to be the United States of America.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action rejects claims 1-4 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants respectfully traverse.

The present application describes a novel G-protein coupled receptor (GPCR). Of the pharmaceutical products currently being market by the entire industry, 60% of these drugs target G-protein coupled receptors (Gurrath, 2001, Curr. Med. Chem. *8*:1257-1299). Given that more than half of the currently marketed drugs target proteins that are structurally (7TM proteins) and functionally (G-protein interaction) related to the presently described sequences, a preponderance of the evidence clearly weighs in favor of Applicants' assertion that the presently described sequences have a specific (the claimed GPCR proteins are encoded by a specific locus on the human genome), credible, and well-established utility.

The Action quotes an article by Ji *et al.* ("Ji"; 1998, J. Biol. Chem. *273*:17299-17302; incorrectly identified in the Action as Tae *et al.*) as teaching that structural homology alone is not a good predictor of function. However, when taken as a whole, Ji, derives and describes structure/function relationships and principles that can be utilized when dealing with G-protein coupled receptors. Thus rather than arguing against the value of structural homology, Ji serves as a clear example of just how extensive the level of knowledge and skill in the art with regard to G-protein coupled receptors was, even, 4 years ago. In addition an exact quote from Ji, a portion of which was used in the Action (page 4), completely undermines this argument: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity" (Ji at 17299, first paragraph, emphasis added). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily - the fact that there is little or no homology between subfamilies is completely irrelevant. The Action next cites an article by Skolnick and Fetrow ("Skolnick"; 2000, TIBTECH 18:34-39) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction

of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used, as described by Ji, to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus arguing against the conclusion drawn in the Action. The Action finally cites Yan *et al.* ("Yan"; 2000, Science 290:523-527) for the proposition that "even a two-amino acid substitution in a molecular structure of a protein can lead to total loss of a protein (*sic*) to bind a specific receptor" (Action at page 4). However, this paper cites only one example, (which is a TNF receptor superfamily protein not a G-protein coupled receptor) two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that to violate § 101 the claimed invention "must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985)) states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Id* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Examiner accepts that the claimed sequence "is an orphan G-Protein coupled receptor" (Action at page 2), but states that this is not indicative of the claimed sequence having a specific, substantial and credible utility, because "further research" would be required to determine the usefulness of the protein (Action at page 5). However, this is incorrect as a matter of law. As the protein of the instant invention belongs to a family of compounds with a common, well established specific and substantial utility, the Federal Circuit's ruling in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is completely on point. In *Brana*, the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted.

The Examiner seems to be requiring data that shows objective evidence that the "instant DNA or encoded protein" is associated with any "diseases or disorders" (Action at page 4). However, as stated above in *Brana*, the Federal Circuit has clearly stated that this is not the standard for utility under

35 U.S.C. § 101. The Examiner states that a "real-world" utility does not require further research (Action at page 5). However, even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

As just one example of utility of the present nucleotide sequences, Applicants point out that, as taught in the specification as originally filed, at least at page 8, the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transaction was $620 million) that it was acquired by large pharmaceutical company, Merck & Co., for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The

sequences of the present invention describe a novel gene encoding a GPCR and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encode human GPCRs, as detailed throughout the specification. The specification also teaches that GPCRs are associated with a wide variety of cellular functions, and as such, that GPCR interacting proteins have been subject to intense scrutiny as potential drug targets. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of the Venter *et al.* article (Science, 2001, *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence

information in the structural analysis of genomic data. The presently claimed polynucleotide sequences define biologically validated sequences that provide a unique and specific resource for mapping genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

As evidence of the credibility of Applicants assertion that the present invention is an GPCR. Applicants submit that a BLASTN analysis of **SEQ ID NO: 3** identifies GenBank accession no. NM_054030 (**Exhibit C**), which has been annotated by third party scientists, wholly unaffiliated with Applicants, as encoding *Homo sapiens* G protein-coupled receptor MRGX2, mRNA (**Exhibit D**). This molecule is nearly identical to SEQ ID NO: 3, the difference being a single nucleic acid at position 786. A series of nnn's can be seen in the query sequence and this masking, also results in a difference. However, since this masking also identifies a difference when the query sequence of SEQ ID NO: 3 is compared to itself (original in house identifier hGPR32 ORF 3: **Exhibit E**) using the same program, indicating that the series of nnn's and the identified difference can therefore be attributed to the BLAST program.

Given this clear evidence that those of skill in the art would recognize the present invention as a GPCR, more specifically MRGX2, whose function is described in the scientific publication entitled "A divers family of GPCRs expressed in specific subsets of nociceptive sensory neurons" (Dong, et al., Cell 106:619-32, 2001; Abstract included as **Exhibit F**). Clearly, there can be no question that Applicants' asserted utility for the described sequences is "credible." Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode a G protein-coupled receptor, in particular that of MRGX2.. In contrast, the Examiner has provided no evidence of record indicating that those of skill in the art would not recognize the sequences of the present invention encode a G protein-coupled receptor. As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35 U.S.C. § 101, and the Examiner's rejection should be withdrawn.

Additionally, methods similar to those of the present invention were used to identify the GPCR of issued U.S. Patent 6,043,052. Issued U.S. Patents are presumed to be valid and to meet the requirements of 35 U.S.C. §§ 101, 102, 103 and 112, specifically, that they have utility, are novel, non-obvious, are enabled, meet the written description requirements and particularly point out and distinctly claim the invention. Therefore, the Applicants' assertion that the described GPCR is in fact a GPCR is supported by issued U.S. Patent 6,043,052, as well as the plethora of other GPCR patents that the office has issued. For example, the specific and substantial utility of human GPCRs is evidenced by the fact that they are the subject of the above mentioned U.S. Patent No. 6,043,052 which discloses polynucleotides encoding a novel GPCR and U.S. Patent Nos. 5,891,646 and 6,110,693, both of which disclose and claim methods for detecting GPCR activity *in vivo* and *in vitro*, methods for assaying GPCR activity, and methods of screening for GPCR ligands, GPCR kinase activity, components that interact with GPCR regulatory processes and constructs useful in such methods. The issuance of these U.S. patents clearly indicates that GPCR polynucleotides have utility and that such utilities were sufficiently specific and substantial to warrant the issuance of U.S. patents directed to methods used to identify and characterize GPCRs. The teachings of these patentable disclosures are directly applicable to the present invention (GPCR polynucleotides) and are evidence that those skilled in the art recognize the specific and substantial

utility of GPCRs. In light of the issuance of U.S. Patent No. 6,043,052 on polynucleotides encoding a novel GPCR, Applicants respectfully submit that the present application, which also describes polynucleotides encoding a novel GPCR, describes an invention with specific and substantial utility fully compliant with 35 U.S.C. § 101.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1-4 under 35 U.S.C. § 101 have been overcome, and request that the rejection be withdrawn.

V. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that claims 1-4 have been shown to have "a specific, substantial, and credible utility", as detailed in section III above. Applicants therefore request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Rejection of Claim 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects Claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse.

First, Applicants in no way agree with the Examiner's position that Claim 1 lacks enablement, as the claim as originally filed is fully operative, to wit, part (b) of the claim requires hybridization to **either** SEQ ID NO:3 or it's complement. As the Examiner admits that "the specification, while being enabling for an isolated nucleic acid molecule which encodes the the amino acid sequence of SEQ ID NO:4 and hybridizes under stringent conditions to the complement of SEQ ID NO:3" (Action at page 5-6), the enablement enquiry should be over, and the rejection of Claim 1 under 35 U.S.C. § 112, first paragraph should be rendered moot. However, solely in order to progress the case more rapidly to allowance, Applicants have amended Claim 1 to recite hybridization to only the complement of SEQ ID NO:1, which the Examiner admits is fully enabled.

The rejection of Claim 1 under 35 U.S.C. § 112, first paragraph has been thus avoided by amendment of Claim 1. Applicants, therefore, respectfully request that the rejection of Claim 1 under 35 U.S.C. § 112, first paragraph be withdrawn.

VII. Rejection of Claims 2, 3 and 4 Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 2-4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification ins such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants submit that this rejection has been avoided by amendment of claims 2, 3 and 4 and addition of new claims 5-7. Therefore, Applicants respectfully request that the rejection of claims 2-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VIII. Rejection of Claim 1 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects Claim 1 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. Specifically, the Action rejects Claim 1 as allegedly indefinite based on the term "stringent hybridization conditions". While Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite "highly stringent hybridization conditions". As the specification provides specific teaching regarding "highly stringent hybridization conditions", at least at page 7, lines 8-15, Applicants submit that revised Claim 1 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Based on the foregoing, Applicants submit that Claim 1 is sufficiently definite, and respectfully request withdrawal of this rejection.

IX. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Chernyshev have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

August 29, 2002

Date

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24231
PATENT TRADEMARK OFFICE

Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/783,669

1. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

   (a) encodes the amino acid sequence shown in SEQ ID NO:4; and

   (b) hybridizes under highly stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 3.

2.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 4.

3.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 2.

4.(Amended) An expression vector comprising a nucleic acid sequence encoding the amino acid sequence shown in SEQ ID NO: 6.

5.(New) A cell comprising the expression vector of Claim 2.

6.(New) A cell comprising the expression vector of Claim 3.

7.(New) A cell comprising the expression vector of Claim 4.